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Control of ovulation in mammals

P.B.D Gonçalves[1], B.G. Gasperin, R. Ferreira, J.T. Santos

Laboratory of Biotechnology and Animal Reproduction, Department of Large Animal Clinic,
Federal University of Santa Maria, RS, Brazil.

Abstract

The ovulatory LH surge induces dramatic molecular and structural changes in follicular environment, culminating with follicle rupture and release of a mature oocyte. This review addresses the pre-LH surge events associated with the ovulatory process, such as dominant follicle differentiation and acquisition of ovulatory capacity, as well as autocrine and paracrine factors induced after the LH surge. Over the last few years, our research group has focused on studying the contribution of renin-angiotensin system in ovulation and the participation of Ang II and Ang-(1-7) and their interactions with factors essential for ovulation, which are also discussed.

Keywords: angiotensin, follicle, LH, ovulation, renin.

Introduction

Ovulation is the apex of follicular development, which begins with the activation of primordial follicles and culminates with the release of a mature oocyte capable of being fertilized and with the formation of a corpus luteum. Ovulation is triggered by the pituitary LH surge, which initiates a series of ovarian events, generating a cascade of paracrine/autocrine factors, enzymes and transcription factors responsible for the rupture of the apical follicle wall, remodeling of extracellular matrix (ECM) and cell differentiation. The understanding of the ovulatory process is essential to elucidate some of the problems associated to female fertility, and to improve technologies applied to animal breeding.

In the present review, we briefly discuss the final stage of dominant follicle differentiation, acquisition of ovulatory capacity and the molecular signals in response to LH, inducing the expression of paracrine and autocrine factors that constitute the preovulatory cascade. We then focus on our recent results showing the importance of Angiotensin II (Ang II) and Angiotensin-(1-7) [Ang-(1-7)] in the control of ovulation in cattle.

Dominant follicle differentiation and acquisition of ovulatory capacity

After bovine follicular deviation, a dominant follicle continues its growth and differentiation and acquires ovulatory capacity at about 12 mm diameter in *Bos taurus taurus* cows, as indicated by the response to LH treatment (Sartori *et al*., 2001). Ovulation of smaller follicles (10 mm) can also be induced, but higher doses of LH are necessary (Sartori *et al*., 2001). The main events associated with final follicle differentiation are acquisition of LH receptors in granulosa cells (Xu *et al*., 1995) and an acute increase in mRNA expression of steroidogenic enzymes HSD3B1 and CYP11A1 in both theca and granulosa cells and CYP17A1 in theca cells (Tian *et al*., 1995). Estradiol synthesis is dramatically increased in the dominant follicle after deviation; however, upregulation of CYP19 mRNA is not observed in granulosa cells (Ferreira *et al*., 2011), suggesting that an increase in aromatizable substrate accounts for the increased steroidogenesis (Tian *et al*., 1995).

Although the exact mechanism leading to final follicular differentiation and ovulatory capacity is not fully understood, several lines of evidences point to a pivotal role for oocyte-secreted factors bone morphogenetic protein 15 (BMP15) and growth and differentiation factor 9 (GDF9). Naturally occurring mutation in ovine BMP15 and GDF9 genes were identified and based on observed phenotypes, it was postulated that the inactivation of one gene and consequently reduced availability of BMP15 or GDF9 affects the differentiation of granulosa cells, inducing precocious differentiation of small antral follicles with fewer granulosa cells (Otsuka *et al*., 2001). In fact, granulosa cells from ewes heterozygous for BMP15 mutation are more responsive to LH, as assessed by cAMP production after hCG treatment (McNatty *et al*., 2009). A mutation in BMPR1B (also known as Alk6) involved in BMP2, 4 and 15 signaling, was also identified in ewes resulting in increased ovulation rate (Mulsant *et al*., 2001; Souza *et al*., 2001). In cattle, Juengel *et al*. (2009) induced multiple ovulations in 6/10 cows immunized against GDF9 and BMP15 peptides, suggesting a function for these proteins in the regulation of follicle differentiation and ovulation rate in this species. Similar results were observed in ewes, in which a significant increase in ovulation rate was induced following BMP15 and GDF9 immunization (McNatty *et al*., 2007). These data point to a role of BMP system in granulosa cell differentiation, but a direct effect of these factors on ovulation process has not been described in monovular species.

Follicular size at ovulation

A wide range of diameter (9-30 mm) is observed in bovine follicles undergoing spontaneous

[1]Corresponding author: bayard@biorep.ufsm.br
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ovulation (Perry *et al*., 2005; Echternkamp *et al*., 2009). The effect of follicle diameter at ovulation on pregnancy rates and endocrine profiles has been extensively studied. It seems that induced but not spontaneous ovulation of smaller follicles is accompanied by reduced pregnancy and embryo viability rates (Perry *et al*., 2005). However, in cattle selected for multiple ovulations, spontaneous ovulation of follicles between 8 and 10 mm is also associated with reduced fertility (Echternkamp *et al*., 2009). It is unknown whether this is due to oocyte or follicular factors.

The main difference between cows ovulating small or large follicles is the pattern of progesterone secretion. Animals experiencing multiple ovulations present smaller ovulatory follicles and corpus luteum (Echternkamp *et al*., 2009). Progesterone levels postovulation are positively associated with follicular diameter at ovulation induction (Atkins *et al*., 2010a, b), but not after spontaneous ovulation (Busch *et al*., 2008). Based on the aforementioned studies, follicle diameter does not seem to influence fertility and progesterone profile in fully differentiated follicles that ovulate spontaneously. Nevertheless, management practices that optimize ovulatory follicle size and differentiation may improve fertility when ovulation is pharmacologically induced.

The effects of LH surge in the early stages of ovulation

At the end of the estrous cycle, the shift in the progesterone/estrogen ratio induces an increase in the GnRH/LH pulse frequency that results in the preovulatory LH surge (Kesner *et al*., 1982). Luteinizing hormone binds to receptors present in the dominant follicle stimulating the classical route of cAMP and protein kinase A (PKA) that induce the expression of paracrine and autocrine factors that trigger the preovulatory cascade (Marsh, 1976; Richards, 1994). The LH receptor (LHCGR) is expressed in granulosa and theca cells, but not in cumulus cells and oocytes (Peng *et al*., 1991, van Tol *et al*., 1996). In rat theca cells, LH stimulates the production of interleukin 1β (IL-1β produced by leukocytes; Kol *et al*., 1999), which is important for cumulus expansion, and induces Insulin-like 3 (Insl-3; Bathgate *et al*., 1999; Kawamura *et al*., 2004). Insl-3 seems to attenuate adenylate cyclase activity, decreasing cAMP in the oocyte, which is essential for meiosis resumption. In granulosa cells LH activates ERK1/2, probably mediated by PKA, resulting in phosphorylation of proteins involved in ovulation, including cAMP response element-binding protein (CREB) and stimulatory proteins 1 and 3 (Sp1/3), which stimulate progesterone receptor (PR), EGF-like factors (EGF-L: amphiregulin, betacellulin and epiregulin), Early growth response-1 (Egr-1), the disintegrin and metalloproteinase with thrombospondin repeats (ADAMTS-1), cathepsin L and versican (Russell and Robker, 2007).

Steroidogenesis is immediately affected and follicular fluid progesterone levels increase 4-5 fold about 1.5 h after the LH surge (Fortune *et al*., 2009), while a gradual decrease in estradiol secretion is observed from 3 h post-GnRH (Santos *et al*., 2011). Progesterone is essential for ovulation (Bridges *et al*., 2006) and oocyte maturation (Siqueira *et al*., 2012a), probably by stimulating the expression of prostaglandin-endoperoxide synthase 2 (PTGS2). Progesterone receptor (PR) antagonists as well as the suppression of the expression of PR or nuclear receptor interacting protein 1 (NRIP1) blocks ovulation and decreases proteases cathepsin L and ADAMTS-1, EGF-L, hyaluronan synthase-2, PTGS2, pentraxin-3-(3-PTX) and tumor necrosis factor stimulator gene-6-(TSG-6) (Russell and Robker, 2007, Robker *et al*., 2000).

The upregulation of PTGS2, characteristic of the ovulation process, suggests that prostanoids are important mediators of LH-induced changes in the ovulatory follicle environment. In fact, intrafollicular injection of an inhibitor of prostanoids synthesis (indomethacin; a potent nonsteroidal anti-inflammatory) blocks the LH-induced increase in PGE2 (Li *et al*., 2006) and inhibits the LH-induced upregulation of amphiregulin (AREG) in theca and granulosa cells, while it negatively affects ADAM17 (a disintegrin and metalloprotease 17) protease in theca cells (Li *et al*., 2009). These results demonstrate that LH-induced AREG and ADAM17 expression in theca cells is prostanoid-dependent. However, the precise function of ADAM17 in theca cells is not clear. ADAMs have been identified as the main sheddases involved in activation and release of EGF-L extracellularly from the cell membrane (Sahin *et al*., 2004). Prostaglandins also seem to increase collagenolytic activity of follicular tissue (as assessed by coincubation with radiolabeled collagen) and proteolytic enzymes such as tissue plasminogen activator (tPA) and plasmin (Li *et al*., 2006; Fortune *et al*., 2009). We must emphasize that these enzymes are essential to digest components of basement membranes, such as collagen type-IV and laminin. Other factors have been identified as being involved in ovulation as phosphodiesterase (PDE), EGF-L, Ang II, plasminogen activators (tPA and uPA), plasmin, and proteases of the extracellular matrix (Robker *et al*., 2000; Curry *et al*., 2001; Park *et al*., 2004; Yang *et al*., 2004; Ferreira *et al*., 2007; Portela *et al*., 2011; Siqueira *et al*., 2012b).

Extracellular matrix remodeling in ovulation

The follicular cells, the basement membrane, the tunica albuginea and the ovarian surface epithelium of the follicle form an organized and stable structure until the preovulatory LH surge. During the process of ovulation, the extracellular matrix of these structures undergoes intense remodeling and revascularization to form the corpus luteum. Enzymes such as matrix

metalloproteinases (MMPs), ADAMTS proteases, plasmin and plasminogen activators (tPA and uPA) are involved (although not all are essential) in remodeling of the extracellular matrix, degrading of the basement membrane and rupturing of the follicular apex (Mittaz *et al*., 2004; Ogiwara *et al*., 2005). Tissue inhibitors of MMPs (TIMPs) are also involved in the ovulatory process and the pattern of *in vivo* expression suggests that decreased TIMPs levels and increased MMPs and PAs are involved in follicle rupture (Li *et al*., 2006). The extracellular matrix remodeling is completed by a process similar to the inflammatory process, with the participation of macrophages, neutrophils, cytokines produced by leukocytes, platelet activating factor and free radicals (Murdoch *et al*., 1999; Wu *et al*., 2004).

Angiotensin II and ovulation

A role for Ang II in ovulation was first postulated based on the increase of the concentration of this peptide and its precursors in the follicular fluid after the LH surge (Yoshimura *et al*., 1994; Acosta *et al*., 2000). The demonstration of the involvement of Ang II in the control of ovulation has been troubled by differences between species and experimental models utilized in different studies (Husain *et al.*, 1987; Pellicer *et al.*, 1988; Daud *et al*., 1989; Yoshimura *et al.*, 1992; Kuji *et al*., 1996). Using *in vitro* and *in vivo* models, we performed a series of experiments to characterize the role of Ang II in bovine ovulation. Two Ang II receptor subtypes have been identified and characterized. The type 1 receptor (AGTR1) mediates a number of well-known Ang II effects on smooth muscle contraction and blood pressure regulation, while the type 2 (AGTR2) receptor has been shown to mediate reproductive functions (Kuji *et al*., 1996; Yoshimura *et al*., 1996). We conducted an experiment to demonstrate that the Ang II signaling participates in the ovulatory cascade. For our surprise, the inhibition of Ang II receptors efficiently blocked ovulation when the receptor blocker was administered before estrus onset (Fig. 1).

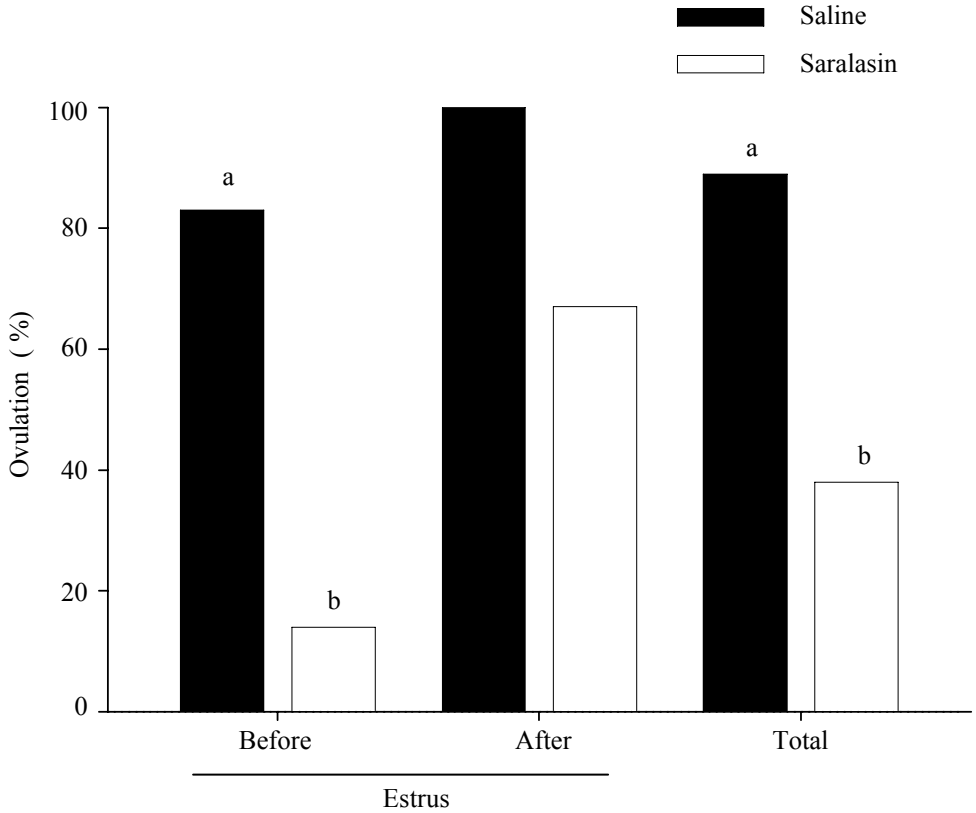

Figure 1. Ovulation rate following ultrasound-mediated intrafollicular injection of saralasin before or after estrus onset. Follicular diameter was at least 12 mm at intrafollicular injection. [a,b]Statistical difference between groups ($P < 0.05$). Figure adapted from Ferreira *et al*., 2007.

Based on the fact that the inhibition of Ang II blocks ovulation only when performed before estrus onset, we hypothesize that Ang II acts at the beginning of the ovulatory cascade in cattle. When an Ang II-receptor antagonist was injected in preovulatory follicles, the ovulation was inhibited only in the first 6 h after GnRH-analogue injection (Fig. 2A). Then, we investigated the receptor type involved in ovulation using an *in vivo* model with intrafollicular injection of specific antagonists. We demonstrated that the effect of Ang II on ovulation is mediated by AGTR2 receptor (Fig. 2B; Ferreira *et al*., 2007).

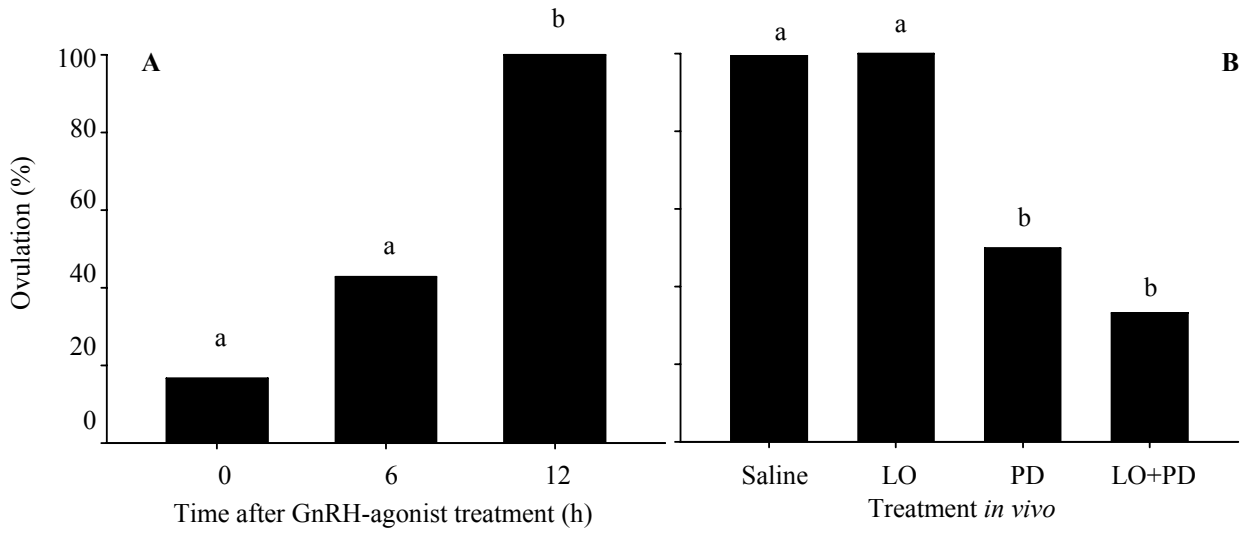

Figure 2. A) Ovulation rate following ultrasound-mediated intrafollicular injection of saralasin at 0, 6, or 12 h after GnRH agonist challenge. B) Effect of angiotensin II type 1 (AGTR1) and type 2 (AGTR2) receptor antagonists on ovulation rate in cow. The animals received an ultrasound-mediated intrafollicular injection of 0.9% NaCl (saline, n = 6), losartan (LO, 10 µl; AGTR1 receptor antagonist; n = 6), PD123 319 (PD, 10 µl; AGTR2 receptor antagonist; n = 6), or 10 µl LO+10 µm PD (n = 6). Follicle diameter was at least 12 mm at intrafollicular injection. Different letters above bars indicate statistical difference between groups ($P < 0.05$). Figure adapted from Ferreira *et al*., 2007.

Angiotensin II levels in preovulatory follicle

In the early 90s, an increase in follicular fluid Ang II levels after LH surge was reported in rodents (Yoshimura *et al*., 1994). Recently, we characterized the changes in Ang II, Ang receptors and Ang II-synthesis related factors during preovulatory period (0, 3, 6, 12 and 24 h after GnRH). The first significant increase in the concentration of Ang II in follicular fluid occurred at 6 h and a dramatic increase at 24 h, after the GnRH injection. Angiotensinogen and angiotensin converting enzyme (factors related to Ang II synthesis) mRNAs were significantly upregulated in granulosa cells (24 h after GnRH) and theca cells (6 h after GnRH), respectively. Immediately after the expected LH surge (3 h after GnRH), an acute increase in AGTR2 mRNA was observed (Siqueira *et al*., 2012b). Taken together these data further confirm that Ang II and renin-angiotensin system (RAS) components are regulated during ovulation.

Angiotensin II in the ovulatory cascade

Angiotensin II has a crucial role in the early events of ovulation, acting through AGTR2 receptors. The challenge is to understand how Ang II interacts with other ovulatory factors and where it is located in the ovulatory cascade. Evidence that Ang II interacts with prostaglandins (PG) was observed when Ang II antagonist blocked the PG synthesis and ovulation in rabbit (Yoshimura *et al*., 1993). The role of PGs in ovulation was first described by Labhsetwar (Labhsetwar, 1971, 1972) and extensively studied during the last decades. Prostaglandins (mainly PGE2) induce vasodilation and tissue changes in the apical region of ovulatory follicle (Kitai *et al*., 1985; Yoshimura *et al*., 1988). Intravenous administration of indomethacin during the ovulatory process decreased PGE2 and PGF2α levels and inhibited ovulation (Espey *et al*., 1986). PTGS2 is upregulated by the LH surge promoting an increase in prostaglandins synthesis (Sirois *et al*., 1992). In PTGS2 knockout mice (Lim *et al*., 1997) and cows submitted to intrafollicular injections of a PTGS2-specific inhibitor (Peters *et al*., 2004) ovulation did not occur normally. *In vitro*, Ang II added to a culture medium containing LH stimulated granulosa cells to secrete 3 to 5 fold more P4, PGE2 and PGF2α compared with controls with or without LH (Siqueira *et al*., 2012b). Taken together, these results suggest that Ang II mediates and enhances the gonadotropin-induced ovulatory cascade at least in part by stimulating the production of prostaglandins.

We also carried out a series of experiments to investigate the involvement of Ang II in the regulation of events upstream of prostaglandins. *In vitro* experiments showed that Ang II can increase the abundance of mRNA encoding disintegrin and ADAM17, AREG and EREG, in the presence of LH. Moreover, the inhibition of ADAM17 sheddase activity abolished the stimulatory effect of Ang II on AREG, EREG and PTGS2 mRNA, suggesting that ADAM17 mediates Ang II action at the beginning of the ovulatory cascade (Portela *et al*., 2011).

Angiotensin-(1-7) and ovulation

Ang-(1-7), an active heptapeptide of the renin-angiotensin system (RAS), was recently identified in the rodent, human and bovine ovaries (Costa *et al*., 2003; Reis *et al*., 2011 Santos *et al*., 2011). This peptide is formed from the cleavage of Ang I and Ang II by angiotensin converting enzyme 2 (ACE2) and prolyl endopeptidase (PEP). In another pathway, Ang-(1-7) is produced from Ang I, which is cleaved by neutral endopeptidase (NEP; Santos *et al*., 1992, Donoghue *et al*., 2000). Ang-(1-7) is cleaved into smaller fragments by ACE and other aminopeptidases, which probably constitutes a mechanism to control its functions (Yamada *et al*., 1998, Chappell *et al*., 2000). Ang-(1-7) actions are mediated by a specific receptor coupled to G protein: MAS (Santos *et al*., 2003, Dilauro and Burns, 2009).

Little is known about the functions of Ang-(1-7) during the ovulation process. Increased expression of MAS and ACE2 mRNA in ovarian homogenates, and immunolocalization of Ang-(1-7) and MAS in theca and interstitial cells in response to gonadotropins were reported (Pereira et al., 2009). In bovine follicles ≥12 mm, the presence of mRNA for MAS, ACE2 NEP and PEP was observed in theca and granulosa cells (Santos *et al*., 2011) and MAS receptor was located to granulosa cells (unpublished data). Moreover, levels of Ang-(1-7) increased 12 h after treatment with GnRH in the follicular fluid (Santos *et al*., 2011), which was probably a consequence of the concomitant increase in ACE2, NEP and PEP mRNA expression in granulosa cells (Santos *et al*., 2011).

Disruption of MAS receptor signaling inhibited gonadotropin induced ovulation in the ovarian perfusion model in rabbits. In addition, Ang-(1-7) was able to induce ovulation and estradiol production in the absence of gonadotropins (Viana *et al*., 2011). However, ovulation was not blocked when MAS receptor signaling was inhibited with intrafollicular injections of A-779 in cows challenged with GnRH (unpublished data). This is different from the results obtained with Ang II receptor blocker (Ferreira *et al*., 2007), suggesting that Ang-(1-7) has a distinct role during the ovulatory process. Interestingly, Ang-(1-7) stimulated arachidonic acid (AA) and prostaglandin in rabbit aortic vascular smooth muscle cells (Muthalif *et al*., 1998) and it is well known that prostaglandins are essential for ovulation (Yoshimura *et al*., 1988; Sirois *et al*., 2004; Fortune *et al*., 2009). Therefore, the results obtained so far suggest that Ang-(1-7) is involved in the regulation of the ovulatory process, although more studies are needed to understand its specific roles.

Final considerations

The ovulation process initiates with LH binding to its receptor and activating ERK1/2 in granulosa cells, probably mediated by PKA and EGF-L, resulting in phosphorylation of proteins important for cell proliferation and differentiation and ECM remodeling. These initial LH effects induce a gradual decrease in estradiol synthesis, increase in progesterone, induction of cumulus expansion, oocyte maturation and follicular rupture. The molecular control of ovulation after the LH surge involves transcription factors, peptides and enzymes that form a cascade resulting in the release of an oocyte capable of being fertilized. We have focused our research on the role of renin-angiotensin system (RAS) in follicular development, ovulation and oocyte maturation using the cow as the animal model as it is a monovulatory species in which ovulation time can be predicted and follicular environment modified *in vivo*. We observed that intrafollicular injection of a competitive antagonist of Ang II impairs ovulation in cows and that Ang II acts via the AGTR2 receptor. We also found that Ang II enhances the LH-induced increase in P4, PGE2 and PGF2α, which are essential for ovulation. Furthermore, we showed that Ang II stimulated the expression/activity of ADAM17, which resulted in upregulation of EGF-L and PTGS2. Taken together, these results demonstrate that RAS is essential for ovulation in cattle.

References

Acosta TJ, Ozawa T, Kobayashi S, Hayashi K, Ohtani M, Kraetzl WD, Sato K, Schams D, Miyamoto A. 2000. Periovulatory changes in the local release of vasoactive peptides, prostaglandin F2α, and steroid hormones from bovine mature follicles in vivo. *Biol Reprod*, 63:1253-1261.

Atkins JA, Smith MF, Wells KJ, Geary TW. 2010a. Factors affecting preovulatory follicle diameter and ovulation rate after gonadotropin-releasing hormone in postpartum beef cows. Part I: cycling cows. *J Anim Sci*, 88:2300-2310.

Atkins JA, Smith MF, Wells KJ, Geary TW. 2010b. Factors affecting preovulatory follicle diameter and ovulation rate after gonadotropin-releasing hormone in postpartum beef cows. Part II: anestrous cows. *J Anim Sci*, 88:2311-2320.

Bathgate R, Moniac N, Bartlick B, Schumacher M, Fields M, Ivell R. 1999. Expression and regulation of relaxin-like factor gene transcripts in the bovine ovary: differentiation-dependent expression in theca cell cultures. *Biol Reprod*, 61:1090-1098.

Bridges PJ, Komar CM, Fortune JE. 2006. Gonadotropin-induced expression of messenger ribonucleic acid for cyclooxygenase-2 and production of prostaglandins E and F2alpha in bovine preovulatory follicles are regulated by the progesterone receptor. *Endocrinology*, 147:4713-4722.

Busch DC, Atkins JA, Bader JF, Schafer DJ, Patterson DJ, Geary TW, Smith MF. 2008. Effect of

ovulatory follicle size and expression of estrus on progesterone secretion in beef cows. *J Anim Sci*, 86:553-563.

Chappell MC, Gomez MN, Pirro NT, Ferrario CM. 2000. Release of angiotensin-(1-7) from the rat hindlimb: influence of angiotensin-converting enzyme inhibition. *Hypertension*, 35:348-352.

Costa APR, Fagundes-Moura CR, Pereira VM, Silva LF, Vieira MAR, Santos RAS, Reis AM. 2003. Angiotensin-(1-7): a novel peptide in the ovary. *Endocrinology*, 144:1942-1948.

Curry TE, Song L, Wheeler SE. 2001. Cellular localization of gelatinases and tissue inhibitors of metalloproteinases during follicular growth, ovulation, and early luteal formation in the rat. *Biol Reprod*, 65:855-865.

Daud AI, Bumpus FM, Husain A. 1989. Angiotensin-II - does it have a direct obligate role in ovulation. *Science*, 245:870-871.

Dilauro M, Burns KD. 2009. Angiotensin-(1-7) and its effects in the kidney. *ScientificWorldJournal*, 9:522-535.

Donoghue M, Hsieh F, Baronas E, Godbout K, Gosselin M, Stagliano N, Donovan M, Woolf B, Robison K, Jeyaseelan R, Breitbart RE, Acton S. 2000. A novel angiotensin-converting enzyme–related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1-9. *Circ Res*, 87:e1-e9.

Echternkamp SE, Cushman RA, Allan MF. 2009. Size of ovulatory follicles in cattle expressing multiple ovulations naturally and its influence on corpus luteum development and fertility. *J Anim Sci*, 87:3556-3568.

Espey LL, Norris C, Saphire D. 1986. Effect of time and dose of indomethacin on follicular prostaglandins and ovulation in the rabbit. *Endocrinology*, 119:746-754.

Ferreira R, Oliveira JF, Fernandes R, Moraes JF, Gonçalves PB. 2007. The role of angiotensin II in the early stages of bovine ovulation. *Reproduction*, 134:713-719.

Ferreira R, Gasperin B, Santos J, Rovani M, Santos RA, Gutierrez K, **Oliveira JF, Reis AM, Gonçalves PB**. 2011. Angiotensin II profile and mRNA encoding RAS proteins during bovine follicular wave. *J Renin Angiotensin Aldosterone Syst*, 12:475-482.

Fortune JE, Willis EL, Bridges PJ, Yang CS. 2009. The periovulatory period in cattle: progesterone, prostaglandins, oxytocin and ADAMTS proteases. *Anim Reprod*, 6:60-71.

Husain A, Bumpus FM, Silva PD, Speth RC. 1987. Localization of angiotensin II receptors in ovarian follicles and the identification of angiotensin II in rat ovaries. *Proc Natl Acad Sci USA*, 84:2489-2493.

Juengel JL, Hudson NL, Berg M, Hamel K, Smith P, Lawrence SB, Whiting L, McNatty KP. 2009. Effects of active immunization against growth differentiation factor 9 and/or bone morphogenetic protein 15 on ovarian function in cattle. *Reproduction*, 138:107-114.

Kawamura K, Kumagai J, Sudo S, Chun S-Y, Pisarska M, Morita H, **Toppari J, Fu P, Wade JD, Bathgate RA, Hsueh AJ**. 2004. Paracrine regulation of mammalian oocyte maturation and male germ cell survival. *Proc Natl Acad Sci USA*, 101:7323-7328.

Kesner JS, Padmanabhan V, Convey EM. 1982. Estradiol induces and progesterone inhibits the preovulatory surges of luteinizing hormone and follicle-stimulating hormone in heifers. *Biol Reprod*, 26:571-578.

Kitai H, Yoshimura Y, Wright KH, Santulli R, Wallach EE. Microvasculature of preovulatory follicles: comparison of in situ and in vitro perfused rabbit ovaries following stimulation of ovulation. *Am J Obstetr Gynecol*, 1985. 152:889-895.

Kol S, Ruutiainen-Altman K, Scherzer WJ, Ben-Shlomo I, Ando M, Rohan RM, Adashi EY. 1999. The rat intraovarian interleukin (IL)-1 system: cellular localization, cyclic variation and hormonal regulation of IL-1β and of the type I and type II IL-1 receptors. *Mol Cell Endocrinol*, 149:115-128.

Kuji N, Sueoka K, Miyazaki T, Tanaka M, Oda T, Kobayashi T, Yoshimura Y. 1996. Involvement of angiotensin II in the process of gonadotropin-induced ovulation in rabbits. *Biol Reprod*, 55:984-991.

Labhsetwar AP. 1971. Luteolysis and ovulation induced by prostaglandin F2-alpha in the hamster. *Nature*, 230:528-529.

Labhsetwar AP. 1972. Luteolytic and ovulation-inducing properties of prostaglandin F2 in pregnant mice. *J Reprod Fertil*, 28451-28452.

Li Q, Jimenez-Krassel F, Kobayashi Y, Ireland JJ, Smith GW. 2006. Effect of intrafollicular indomethacin injection on gonadotropin surge-induced expression of select extracellular matrix degrading enzymes and their inhibitors in bovine preovulatory follicles. *Reproduction*, 131:533-543.

Li Q, Jimenez-Krassel F, Ireland JJ, Smith GW. 2009. Gene expression profiling of bovine preovulatory follicles: gonadotropin surge and prostanoid-dependent up-regulation of genes potentially linked to the ovulatory process. *Reproduction*, 137:297-307.

Lim H, Paria BC, Das SK, Dinchuk JE, Langenbach R, Trzaskos JM, Dey SK. 1997. Multiple female reproductive failures in cyclooxygenase 2-deficient mice. *Cell*, 91:197-208.

Marsh JM. 1976. The role of cyclic AMP in gonadal steroidogenesis. *Biol Reprod*, 14:30-53.

McNatty KP, Hudson NL, Whiting L, Reader KL, Lun S, Western A, Heath DA, Smith P, Moore LG, Juengel JL. 2007. The effects of immunizing sheep with different BMP15 or GDF9 peptide sequences on ovarian follicular activity and ovulation rate. *Biol Reprod*, 76:552-560.

McNatty KP, Heath DA, Hudson NL, Lun S, Juengel JL, Moore LG. 2009. Gonadotrophin-responsiveness of granulosa cells from bone morphogenetic protein 15 heterozygous mutant sheep. *Reproduction*, 138:545-551.

Mittaz L, Russell DL, Wilson T, Brasted M, Tkalcevic J, Salamonsen LA, Hertzog PJ, Pritchard MA. 2004. Adamts-1 is essential for the development and function of the urogenital system. *Biol Reprod*, 70:1096-1105.

Mulsant P, Lecerf F, Fabre S, Schibler L, Monget P, Lanneluc I, **Pisselet C, Riquet J, Monniaux D, Callebaut I, Cribiu E, Thimonier J, Teyssier J, Bodin L, Cognié Y, Chitour N, Elsen JM**. 2001. Mutation in bone morphogenetic protein receptor-IB is associated with increased ovulation rate in Booroola Merino ewes. *Proc Natl Acad Sci USA*, 98:5104-5109.

Murdoch WJ, Wilken C, Young DA. 1999. Sequence of apoptosis and inflammatory necrosis within the formative ovulatory site of sheep follicles. *J Reprod Fertil*, 117:325-329.

Muthalif MM, Benter IF, Uddin MR, Harper JL, Malik KU. 1998. Signal transduction mechanisms involved in angiotensin-(1–7)-stimulated arachidonic acid release and prostanoid synthesis in rabbit aortic smooth muscle cells. *J Pharmacol Exp Ther*, 284:388-398.

Ogiwara K, Takano N, Shinohara M, Murakami M, Takahashi T. 2005. Gelatinase A and membrane-type matrix metalloproteinases 1 and 2 are responsible for follicle rupture during ovulation in the medaka. *Proc Natl Acad Sci USA*, 102:8442-8447.

Otsuka F, Yamamoto S, Erickson GF, Shimasaki S. 2001. Bone morphogenetic protein-15 Inhibits follicle-stimulating hormone (FSH) action by suppressing FSH receptor expression. *J Biol Chem*, 276:11387-11392.

Park J-Y, Su Y-Q, Ariga M, Law E, Jin S-LC, Conti M. 2004. EGF-like growth factors as mediators of l h action in the ovulatory follicle. *Science*, 303:682-684.

Pellicer A, Palumbo A, DeCherney AH, Naftolin F. 1988. Blockage of ovulation by an angiotensin antagonist. *Science*, 240:1660-1661.

Peng X-R, Hsueh AJW, Lapolt PS, Bjersing L, Ny T. 1991. Localization of luteinizing hormone receptor messenger ribonucleic acid expression in ovarian cell types during follicle development and ovulation. *Endocrinology*, 129:3200-3207.

Pereira VM, Reis FM, Santos RA, Cassali GD, Santos SH, Honorato-Sampaio K, Reis AM. 2009. Gonadotropin stimulation increases the expression of angiotensin-(1-7) and MAS receptor in the rat ovary. *Reprod Sci*, 16:1165-1174.

Perry GA, Smith MF, Lucy MC, Green JA, Parks TE, MacNeil MD, Roberts AJ, Geary TW. 2005. Relationship between follicle size at insemination and pregnancy success. *Proc Natl Acad Sci USA*, 102:5268-5273.

Peters MW, Pursley JR, Smith GW. 2004. Inhibition of intrafollicular PGE2 synthesis and ovulation following ultrasound-mediated intrafollicular injection of the selective cyclooxygenase-2 inhibitor NS-398 in cattle. *J Anim Sci*, 82:1656-1662.

Portela VM, Zamberlam G, Gonçalves PBD, de Oliveira JFC, Price CA. 2011. Role of angiotensin II in the periovulatory epidermal growth factor-like cascade in bovine granulosa cells in vitro. *Biol Reprod*, 85:1167-1174.

Reis FM, Bouissou DR, Pereira VM, Camargos AF, dos Reis AM, Santos RA. 2011. Angiotensin-(1-7), its receptor Mas, and the angiotensin-converting enzyme type 2 are expressed in the human ovary. *Fertil Steril*, 95:176-181.

Richards JS. 1994. Hormonal control of gene expression in the ovary. *Endocr Rev*, 15:725-751.

Robker RL, Russell DL, Espey LL, Lydon JP, O'Malley BW, Richards JS. 2000. Progesterone-regulated genes in the ovulation process: ADAMTS-1 and cathepsin L proteases. *Proc Natl Acad Sci USA*, 97:4689-4694.

Russell DL, Robker RL. 2007. Molecular mechanisms of ovulation: co-ordination through the cumulus complex. *Hum Reprod Update*, 13:289-312.

Sahin U, Weskamp G, Kelly K, Zhou HM, Higashiyama S, Peschon J, Hartmann D, Saftig P, Blobel CP. 2004. Distinct roles for ADAM10 and ADAM17 in ectodomain shedding of six EGFR ligands. *J Cell Biol*, 164:769-779.

Santos JT, Ferreira R, Gasperin BG, Siqueira LC, de Oliveira JF, Santos RA, Reis AM, Gonçalves PB. 2012. Molecular characterization and regulation of the angiotensin-converting enzyme type 2/Angiotensin-(1-7)/MAS receptor axis during the ovulation process in cattle. *J Renin Angiotensin Aldosterone S*yst,13:91-98.

Santos RA, **Brosnihan KB, Jacobsen DW, DiCorleto PE, Ferrario CM**. 1992. Production of angiotensin-(1-7) by human vascular endothelium. *Hypertension*, 19(suppl):II56-II61.

Santos RAS, Silva ACSE, Maric C, Silva DMR, Machado RP, de Buhr I, Heringer-Walther S, Pinheiro SV, Lopes MT, Bader M, Mendes EP, Lemos VS, Campagnole-Santos MJ, Schultheiss HP, Speth R, Walther T. 2003. Angiotensin-(1-7) is an endogenous ligand for the G protein-coupled receptor mas. *Proc Natl Acad Sci USA*, 100:8258-8263.

Sartori R, Fricke PM, Ferreira JCP, Ginther OJ, Wiltbank MC. 2001. Follicular deviation and acquisition of ovulatory capacity in bovine follicles. *Biol Reprod*, 65:1403-1409.

Siqueira LC, Barreta MH, Gasperin B, Bohrer R, Santos JT, Buratini Jr J, Oliveira JF, Gonçalves PB. 2012a. Angiotensin II, progesterone, and prostaglandins are sequential steps in the pathway to bovine oocyte nuclear maturation. *Theriogenology*, 77:1779-1787.

Siqueira LC, Santos JT, Ferreira R, Santos R, Reis A, Oliveira JF, Fortune JE, Gonçalves PB. 2012b. Preovulatory changes in the angiotensin II system in bovine follicles. *Reprod Fertil Dev*. Doi: 10.1071/ RD11316. Available on: http://www.publish.csiro.au/ paper/RD11316.htm.

Sirois J, Simmons DL, Richards JS. 1992. Hormonal regulation of messenger ribonucleic acid encoding a novel isoform of prostaglandin endoperoxide H

synthase in rat preovulatory follicles. Induction in vivo and in vitro. *J Biol Chem*, 267:11586-11592.

Sirois J, Sayasith K, Brown KA, Stock AE, Bouchard N, Doré M. 2004. Cyclooxygenase-2 and its role in ovulation: a 2004 account. *Hum Reprod Update*, 10:373-385.

Souza C, MacDougall C, Campbell B, McNeilly A, Baird D. 2001. The Booroola (FecB) phenotype is associated with a mutation in the bone morphogenetic receptor type 1 B (BMPR1B) gene. *J Endocrinol*, 169:R1-R6.

Tian XC, Berndtson AK, Fortune JE. 1995. Differentiation of bovine preovulatory follicles during the follicular phase is associated with increases in messenger ribonucleic acid for cytochrome P450 side-chain cleavage, 3 beta-hydroxysteroid dehydrogenase, and P450 17 alpha-hydroxylase, but not P450 aromatase. *Endocrinology*, 136:5102-5110.

van Tol HTA, van Eijk MJT, Mummery CL, van Den Hurk R, Bevers MM. 1996. Influence of FSH and hCG on the resumption of meiosis of bovine oocytes surrounded by cumulus cells connected to membrane granulosa. *Mol Reprod Dev*, 45:218-224.

Viana GEN, Pereira VM, Honorato-Sampaio K, Oliveira CA, Santos RAS, Reis AM. 2011. Angiotensin-(1–7) induces ovulation and steroidogenesis in perfused rabbit ovaries. *Exp Physiol*, 96:957-965.

Wu R, Van der Hoek KH, Ryan NK, Norman RJ, Robker RL. 2004. Macrophage contributions to ovarian function. *Hum Reprod Update*, 10:119-133.

Xu Z, Garverick HA, Smith GW, Smith MF, Hamilton SA, Youngquist RS. 1995. Expression of follicle-stimulating hormone and luteinizing hormone receptor messenger ribonucleic acids in bovine follicles during the first follicular wave. *Biol Reprod*, 53:951-957.

Yamada K, Iyer SN, Chappell MC, Ganten D, Ferrario CM. 1998. Converting enzyme determines plasma clearance of angiotensin-(1-7). *Hypertension*, 32:496-502.

Yang W-L, Godwin AK, Xu X-X. 2004. Tumor necrosis factor-α-induced matrix proteolytic enzyme production and basement membrane remodeling by human ovarian surface epithelial cells. *Cancer Res*, 64:1534-1540.

Yoshimura Y, Dharmarajan AM, Gips S, Adachi T, Hosoi Y, Atlas SJ, Wallach EE. 1988. Effects of prostacyclin on ovulation and microvasculature of the in vitro perfused rabbit ovary. *Am J Obstetr Gynecol*, 159:977-982.

Yoshimura Y, Karube M, Koyama N, Shiokawa S, Nanno T, Nakamura Y. 1992. Angiotensin II directly induces follicle rupture and oocyte maturation in the rabbit. *FEBS Lett*, 307:305-308.

Yoshimura Y, Karube M, Oda T, Koyama N, Shiokawa S, Akiba M, Yoshinaga A, Nakamura Y. **1993**. Locally produced angiotensin II induces ovulation by stimulating prostaglandin production in in vitro perfused rabbit ovaries. *Endocrinology*. 133:1609-1616

Yoshimura Y, Koyama N, Karube M, Oda T, Akiba M, Yoshinaga A, Shiokawa S, Jinno M, Nakamura Y. **1994**. Gonadotropin stimulates ovarian renin-angiotensin system in the rabbit. *J Clin Invest*, 93:180-187.

Yoshimura Y, Karube M, Aoki H, Oda T, Koyama N, Nagai A, Akimoto Y, Hirano H, Nakamura Y. 1996. Angiotensin II induces ovulation and oocyte maturation in rabbit ovaries via the AT2 receptor subtype. *Endocrinology*, 137:1204-1211.